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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/794,851	02/04/97	MARANY	F 19603/461(CR

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MICHAEL L. GOLDMAN
NIXON HARGRAVE DEVANS AND DOYLE
CLINTON SQUARE
P O BOX 1051
ROCHESTER NY 14603

EXAMINER	
RICIGLIANO,J	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/10/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/794,851	Applicant(s) Barany et al.
	Examiner Joseph W. Ricigliano Ph. D.	Group Art Unit 1618

☒ Responsive to communication(s) filed on *Aug 27, 1998* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-66, 75-88, and 138-147* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-66, 75-88, and 138-147* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This action is responsive to the amendment of June 19, 1998 (paper number 10) and the supplementary amendment of August 27, 1998 (paper number 16).

2. Claims 1-147 are pending in the instant application . Claims 67-74 and 88-137 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-66, 75-88 and 138-147 are currently being examined on the merits.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) for reasons of record in the office action of 12/16/97, paper number 7.

5. Claims 6-10, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994)as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra* in further view Telenti et al for reasons of record in the office action of 12/16/97, paper number 7.

6. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra*, in further view of Barany (1991b) for reasons of record in the office action of 12/16/97, paper number 7.

7. Claims 78, 82, 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) supra in further view of Sambrook et al for reasons of record in the office action of 12/16/97, paper number 7.

Response to Arguments

8. Applicant's arguments filed June 19, 1998 (paper number 10) and August 27, 1998 (paper number 16) have been fully considered but they are not persuasive.

9. Claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) for reasons of record in the office action of 12/16/97, paper number 7.

Applicants first assert that Wiedmann clearly differentiates LCR from LDR and second asserts that Wiedmann, Barany and Guo reference do not teach LDR in conjunction with a

capture support or array. Applicants further assert that the Zaun reference teaches "at most" gap-LCR which applicants assert is more than just a difference in methodology but results in a significant impact on the utility of each technique. With respect to applicants first assertion, The argument is not found persuasive because Wiedmann et al while distinguishing between LCR and LDR explicitly recites LDR as "similar to LCR" and references the Barany publication cited above. The Barany publication clearly teaches that. "Thermostable ligase discriminated single-base mismatches under both LDR and LCR conditions..." Therefore one of skill in the art would have known that either method with could be employed for the sensitive detection required in instant claims.

With respect to applicants second assertion it is noted that applicant is attacking the references individually rather than for their combined teachings. The Barany and Wiedmann references as combined teach the close relationship between LCR and LDR as discussed above, albeit that one process produces a dsDNA product and the other a ssDNA. In that anyone of ordinary skill in the art would recognize that this it is of no consequence because the strands can simply be denatured prior to hybridization at their target site. (In addition it is noted that strand pairs are separated at every cycle of ligase amplification processes by thermal denaturation or "melting." Hence, it must be obvious and within the skill of one carrying out ligase mediated reaction how to separate and hybridize the amplified strands.) In combination with Zaun the above references teach that it is known in the art how to capture an amplification product from a ligase mediated amplification procedure. Applicants' lengthy discourse spanning pages 8-10 of

their June 25th response concerning the differences between LDR, LCR and gap-LCR, which is used in the Zaun reference is not persuasive because applicant appears to be trying to limit Zaun to his exemplified embodiments not his broader teaching of LCR use. Furthermore, Zaun was not relied on for teaching the relevant amplification techniques, the Barany and Wiedmann references teach LDR and it relationship to LCR. Moreover, once amplified, the all three processes produce fundamentally the same product, a ligated DNA strand albeit ss or ds as discussed above, and one of ordinary skill in the art would know when to utilize the appropriate variations of ligase mediated amplifications because the prior art cited teaches this. Hence, the detection system as disclosed by Zaun et al would be capable of detecting the products of nucleic acid amplification reactions.

Applicants' assertion beginning on page 10 of their 6/25/98 response that Zaun et al does not provide an enabling disclosure of hybridization capture procedure or the use of addressable array specific portions has been fully considered and not found persuasive. The argument is not found persuasive because applicant is arguing limitations not present in the claims. The claims are either not limited to nucleic acid array-specific portions (see for example claim 1, which recites "a first oligonucleotide probe, having a target specific portion and an address array specific portion") or when limited to nucleic acid addressable array-specific portions (e.g. claim 7), the limitation that the array specific portion be different from the target sequence or a portion thereof is not present. Second, applicant is again reminded they are attacking the references independently. Applicant is directed to the Guo reference where hybridization of addressable

array specific portions of amplified nucleic acids to an array of capture nucleic aids is taught at length.

Thus the references as combined teach that is obvious to capture a nucleic acid amplification product, from PCR, LCR gap-LCR or LDR using an addressable array and render the claims of the instant application obvious.

With respect the applicants assertion that clams 11-34 are not rendered obvious on page 11 because they feel there is a lack of teachings in the cited references:

Applicants are directed to:

Quantification; See page 12 of the office action note the teachings of the Zaun et al at and Guo et al references, particularly Guo et al for quantitation (see the entire document especially pages 5462-3 under the "Quantitative Image Analysis."

Oligonucleotide primers with substantially the same mp. See page 11 of the office action where the examiner recited the melting points in the table of page 9 in the Barany reference for this teaching

Detecting multiple allele differences is implicitly taught in the Barany reference at page 7 where he states "Thermostable ligase discriminated single-base mismatches under both LDR and LCR conditions..." Barany goes on to teach the detection of alleles and exemplifies this with beta globin (Figs 1 & 2 and table 1) using LCR. In view of these teaching and Wiedmann's teaching that LCR and LDR techniques are similar, it is obvious to detect multiple alleles with LDR.

With respect to a mismatch adjacent to the ligation junction. Applicants are directed to the

Barany and Wiedmann references which are replete with statements indicating that for the ligation reaction to occur the oligonucleotides must hybridize with the target to from a ligation junction. Thus it would be obvious to one of ordinary skill in the art that a mismatch adjacent to the ligation junction would interfere with hybridization at the junction and hence the ligation process.

10. Claims 6-10, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994)as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra* in further view Telenti et al for reasons of record in the office action of 12/16/97, paper number 7.

11.Applicants have traversed this rejection because Telenti et al is directed to the use of PCR rather than LDR and that Telenti's PCR procedure is not readily adaptable to the LDR procedure of the present invention. Applicant's arguments filed 6/25/98 have been fully considered but they are not persuasive because Tenenti et al clearly establish that the use of internal standards in nucleic acid amplifications reactions was known in the art at the time of applicants' filing. The fact that one technique is exponential and the other is linear is moot and it is clear that one of ordinary skill in the art would clearly recognized that LDR primers should be used in an LDR reaction.

12. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88

and 138-147 *supra*, in further view of Barany (1991b) for reasons of record in the office action of 12/16/97, paper number 7.

Applicants' state their traversal is similar to that applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 under 35 U.S.C. 103(a). In view of the fact that this rejection is being maintained and in that applicants have provided no specific arguments, the rejection of claim 44 is maintained.

13. Claims 78, 82, 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) supra in further view of Sambrook et al for reasons of record in the office action of 12/16/97, paper number 7.

14. Applicant's arguments filed 6/25/98 have been fully considered but they are not persuasive. Applicants have traversed the rejection because Sambrook et al do not teach the use of LDR products as combined with hybridization. This argument is not found persuasive because the products of LDR, after all is said and done, are nucleic acids and the teaching of Sambrook et al clearly relate to hybridization of nucleic acids.

15. Response to applicants' declaration and remarks of August 27, 1998.

Applicants' incorporate a lengthy discourse into both the declaration and remarks filed 8/27 /98 concerning the need to detect subtle variations in nucleic acids to determine the presence of alleles associated with disease states. These assertions are not contradicted in any way by the

examiner nor are they relevant to the obviousness rejection Set forth in the office action of 12/16/97.

As applicants have asserted that their invention is drawn to PCR/LDR in conjunction with array capture of the ligation products, and that this is nonbvious over the prior art (See page 6 of the remarks). Because the use of ligase mediated amplification reactions is clearly set forth in the prior art (including PCR/LDR) for the detection of even subtle differences in nucleic acids such as allelic differences (see fig.2 Wiedmann et al and the related to the use of ligase mediated amplification to detect various nucleic acids and subtle variants), the use of these technologies for detecting nucleic acids and subtle variants cannot be novel or unobvious. The combination of detecting ligase amplification product using an array addressable nucleic acids is obvious as the resulting products of a ligase mediated amplification reaction are nucleic acids and it is clearly established in the art how to detect nucleic acids using an immobilized array as set forth in the preceding office action and in the arguments above.

Applicants' further assert in their remarks and declaration that their addressable arrays provide superior result. However, applicants are arguing these results for specific embodiments of their capture arrays system, such as at page 12 of the declaration. The invention as claimed is not limited to these embodiments. Therefore, amendment and declaration of 8/27/98 fail to over come the rejections as set forth because they fail to provide a showing commensurate in scope with the invention as claimed.

16. Applicants' arguments and discussion with respect to references not cited as art applied against the instant claims are noted but have not been commented upon as they are not immediately relevant to the rejections of record.

Therefore, claims 1-66, 75-88 and 138-147 are rejected for the reasons of record in paper number 7 and for the reasons above.

NEW GROUNDS OF REJECTION

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.***

18. Claim 12, 16, 18, 19, 20, 22, 26, 30, 34 and 44 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 44 as amended recites the use of a matched verses mismatched oligo nucleotide sets for determining the rate of formation of product sequences. This is vague and indefinite because it is unclear what constitutes a mismatched oligonucleotide product set. Therefore, it is not possible to determine the metes and bounds of the claims as recited. If applicant intends this to be a single base mismatch in a base pair at the site of ligation applicant should amend the claims to explicitly recite this

20. Claims 12, 16, 18, 19, 20, 22, 26, 30 and 34 recite the "nucleotides positions which require overlapping oligonucleotide probe sets." This vague and indefinite because it is unclear when positions require overlapping probe sets.

21. Claim 81 recites the limitation each capture oligonucleotide differs from its adjacent capture oligonucleotide on the array by at least one out of ever four of the nucleotides when the nucleotides are aligned end to end. This is vague and indefinite because it is unclear how to compare oligonucleotides that are different in length or how to align them when different in length.

22. No claims are allowed

Conclusion

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. It is noted by the examiner that the supplemental IDS statements filed under 197c listed numerous references. Only US 5,695,934 and EP 439 182 were provided and hence considered. The remaining six references were not considered due to their absence from the case.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

26. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph. D., can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

DONALD E. ADAMS
SUPERVISORY PATENT EXAMINER